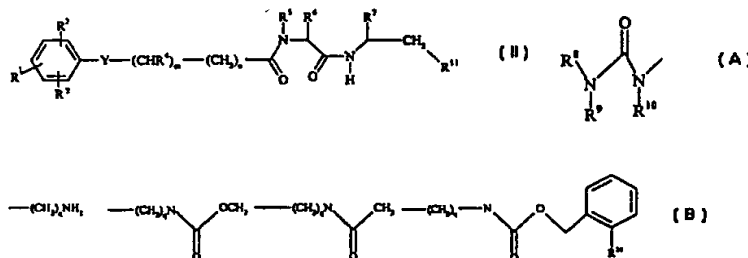




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 275/34, C07D 317/60, C07C 317/50, C07D 405/12, 407/12, 409/12, 417/12, 413/12, C07C 323/60, C07K 5/02, A61K 31/195, 31/36, 31/41		A3	(11) International Publication Number: WO 99/24398
			(43) International Publication Date: 20 May 1999 (20.05.99)
(21) International Application Number: PCT/GB98/03334			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 9 November 1998 (09.11.98)			
(30) Priority Data: 9723789.5 12 November 1997 (12.11.97) GB			
(71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).			
(72) Inventors; and (75) Inventors/Applicants (for US only): BRITTAİN, David, Robert [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). JOHNSTONE, Craig [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).			
(74) Agent: BRYANT, Tracey; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).			Published <i>With international search report.</i>
			(88) Date of publication of the international search report: 5 August 1999 (05.08.99)

(54) Title: UREA DERIVATIVES AND THEIR USE AS INTEGRIN INHIBITORS**(57) Abstract**

Compounds of formula (II) where R^1 is in the para or meta position and is (A); R^2 and R^3 are each independently selected from hydrogen, nitro, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} alkoxyl, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkyl C_{1-4} alkoxyl, C_{1-6} alkylamino C_{1-6} alkyl, amino, cyano, halogeno, trifluoromethyl, $-CO_2R^{12}$ and $-CONR^{12}R^{13}$, where R^{12} and R^{13} are independently selected from hydrogen or C_{1-6} alkyl, or R^2 and R^3 together with the phenyl to which they are attached form a 9 or 10 membered bicyclic ring system; R^4 is C_{1-4} alkyl; R^5 is selected from hydrogen and C_{1-4} alkyl; R^6 is selected from C_{1-6} alkyl, C_{1-6} alkyl(C_{4-6})cycloalkyl, C_{1-6} alkyl(C_{1-6})alkoxyl, C_{1-6} alkylS(C_{1-6})alkyl, C_{1-6} alkylsulphonyl(C_{1-4})alkyl; (B) where q is an integer from 1 to 6 and R^{14} is halogeno; R^7 is selected from C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, C_{2-6} alkenyl, 1,3-benzodioxol-5-yl and aryl each optionally substituted by one or more substituents selected from C_{1-4} alkoxy, C_{1-6} alkyl, cyano, halogeno, and trifluoromethyl; R^8 is aryl, heteroaryl, a bicyclic heteroaryl ring system linked to the nitrogen via a ring carbon or a 9 or 10 membered bicyclic ring system linked to the nitrogen via a ring carbon and each ring is optionally substituted with up to two substituents, which may be the same or different, and are selected from C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl C_{1-4} alkoxyl, C_{1-6} alkylamino C_{1-6} alkyl, hydroxy, $-CO_2H$, $-(CH_2)_pOH$ where p is 1 or 2, cyano, halogeno, and trifluoromethyl; R^9 and R^{10} are each independently selected from hydrogen and C_{1-4} alkyl or R^8 and R^9 together with the nitrogen to which they are attached form a dihydroindolyl, or a dihydroquinolinyl group; R^{11} is selected from carboxyl, tetrazolyl, alkyl sulphonylcarbonyl, sulfo and sulfinyl; Y is oxygen, sulphur or sulfonyl; m is 0 or 1; and n is 0 or an integer from 1 to 4 with the proviso that when m and n cannot both be 0 and when m is 1, n is 0; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof. The compounds inhibit the interaction of vascular cell-adhesion molecule-1 and fibronectin with integrin very late antigen 4 ($\alpha_4\beta_1$). They have therapeutic applications such as in multiple sclerosis, rheumatoid arthritis, asthma, coronary artery disease and psoriasis.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

Inter. Application No

PCT/GB 98/03334

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C275/34 C07D317/60 C07C317/50 C07D405/12 C07D407/12
C07D409/12 C07D417/12 C07D413/12 C07C323/60 C07K5/02
A61K31/195 A61K31/36 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 22966 A (BIOGEN INC) 1 August 1996 cited in the application see table 1; claims 1, 28-33 ---	1,6,8-10
A	WO 97 08145 A (G.D. SEARLE & CO) 6 March 1997 see page 4, line 18 - page 13, line 6; examples 108, 124 -----	1,6,8-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

12 May 1999

Date of mailing of the international search report

21/05/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Van Amsterdam, L

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/03334

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-9
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 8-9
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 98/03334

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9622966 A	01-08-1996	AU 4911596 A	14-08-1996
		BG 101841 A	30-04-1998
		BR 9606778 A	06-01-1998
		CA 2211181 A	01-08-1996
		CN 1177343 A	25-03-1998
		CZ 9702340 A	18-03-1998
		EP 0805796 A	12-11-1997
		FI 973087 A	22-09-1997
		HU 9702461 A	28-04-1998
		JP 10513160 T	15-12-1998
		NO 973384 A	19-09-1997
		PL 321848 A	22-12-1997
		SK 98797 A	04-02-1998
WO 9708145 A	06-03-1997	AU 702487 B	25-02-1999
		AU 7103996 A	19-03-1997
		CA 2230209 A	06-03-1997
		CN 1201454 A	09-12-1998
		CZ 9800341 A	16-09-1998
		EP 0850221 A	01-07-1998
		NO 980817 A	24-04-1998
		NZ 318926 A	29-04-1999
		PL 325312 A	20-07-1998